

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61F 13/02	A1	(11) International Publication Number: WO 95/01767 (43) International Publication Date: 19 January 1995 (19.01.95)
<p>(21) International Application Number: PCT/US94/07544</p> <p>(22) International Filing Date: 6 July 1994 (06.07.94)</p> <p>(30) Priority Data: 08/088,877 8 July 1993 (08.07.93) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 08/088,877 (CIP) Filed on 8 July 1993 (08.07.93)</p> <p>(71) Applicant (for all designated States except US): CYGNUS THERAPEUTIC SYSTEMS [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): WONG, Ooi [MY/US]; 2236 Gomes Road, Fremont, CA 94536 (US). NGUYEN, Thuyticia, N. [US/US]; 2557 Oliver Drive, Hayward, CA 94545 (US).</p> <p>(74) Agents: KENNEDY, Bill et al.; Morrison & Foerster, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).</p>		<p>(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: MONOLITHIC MATRIX TRANSDERMAL DELIVERY SYSTEM</p> <p>(57) Abstract</p> <p>Monolithic matrix formulations for transdermal administration of an active agent, include in combination as a copolymer 2-ethylhexyl acrylate, 2-hydroxyethyl methacrylate, and methacrylic acid. Transdermal delivery devices having a monolithic matrix (4) made using such a formulation in combination with an active agent and a vehicle or vehicle formulation are capable of delivering the active agent at skin flux rates suitable for transdermal administration of the active agent.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

5 MONOLITHIC MATRIX TRANSDERMAL DELIVERY SYSTEM

Background of the Disclosure

Technical Field

10 This invention relates to transdermal drug delivery.

Background Art

1. Monolithic Matrix Delivery Devices.

Transdermal delivery has become an increasingly acceptable mode for
15 administration of prescription and nonprescription drugs, and considerable
effort has been expended toward development of transdermal drug delivery
systems. A number of drugs have reached the market in transdermal delivery
form, most popularly in the form of an adhesive patch.

Essentially, the methodology of transdermal drug delivery involves
20 placing the drug on the skin surface and allowing the drug to permeate through
the skin. Transdermal delivery devices employ a structure that serves as a
reservoir for the drug and that provides for bringing the drug into diffusive
communication with the skin surface. In one general type, the structure
includes a three-dimensionally stable matrix material having a discrete size and
25 shape; such a structure may be referred to as a "monolithic matrix".

A variety of monolithic matrix formulations have been proposed for use
in transdermal delivery systems.

- 2 -

U.S. Patent No. 5,149,538 describes transdermal delivery of opioids using an adhesive matrix prepared from polymers and copolymers of acrylic esters or methacrylic esters and copolymers of acrylic esters or methacrylic esters and other ethylenically-unsaturated monomers. Preferred acrylic
5 adhesives are butyl acrylate, ethyl acrylate, ethyl hexyl acrylate, vinylacetate/ethylene acrylate and mixtures of these.

U.S. Patent No. 4,956,171 describes using sucrose cocoate and methyl laurate for permeation enhancement in transdermal delivery of buprenorphine HCl or hydromorphone HCl, in an adhesive matrix made up of polyacrylic
10 polymers or vinyl acetate-acrylic polymers, and, particularly, a vinyl acetate-acrylic multipolymer solution marketed by Monsanto Co. under the name Gelva ® 788.

German Patent Publications DE 38 43 239 and DE 38 43 238 describe transdermal delivery of physostigmine using a polymer matrix made up, in one
15 example, of an acrylate copolymer of 2-ethylhexyl acrylate, vinyl acetate, and acrylic acid; a methacrylate copolymer of dimethylaminoethyl methacrylate and neutral methacrylic acid esters; and a triglyceride of capryl/caprinacids.

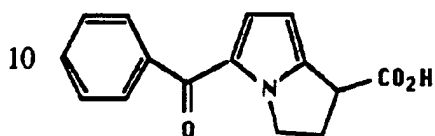
International Application No. PCT/US86/00789 (WO 86/06281) describes a pressure-sensitive adhesive tape for transdermal delivery of
20 nitroglycerin, having a pressure-sensitive adhesive coating made up of an acrylic adhesive copolymer including as a major constituent a hydrophobic monomeric acrylic or methacrylic acid ester of a C₄₋₁₀ alkyl alcohol; and including a reinforcing monomer selected from acrylic acid, methacrylic acid, C₁₋₃ alkyl acrylate or methacrylate, acrylamide, methacrylamide, t-butyl
25 acrylamide, diacetone acrylamide, vinyl ether, substituted ethylene, and vinyl ester.

- 3 -

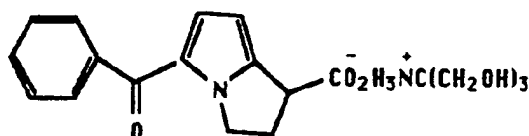
European Patent Publication No. EP 0 481 443 A1 describes a transdermal delivery system having a polymeric matrix made up of a acrylic polymer 7927 79 Röhm-Pharma.

2. Ketorolac tromethamine.

5 Ketorolac is a pyrrolizine carboxylic acid derivative. Combined with tromethamine, ketorolac forms a salt ("ketorolac tromethamine"), which has greater aqueous solubility than ketorolac. The chemical structure of ketorolac and ketorolac tromethamine are shown below:



Ketorolac



Ketorolac Tromethamine

15 Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug useful for short-term management of moderate to severe pain. Ketorolac tromethamine is available *via* prescription in oral tablet form (10 mg strength) and in intramuscular injection form (30 mg/ml).

20 Ketorolac tromethamine has a chiral center and is used as a racemate marketed under the name Toradol; the (-)-S isomer has many times greater analgesic potency than the (+)-R isomer (A. Guzman *et al.*, 1986). Ketorolac tromethamine is an off-white crystalline powder and has a pK_a value of 3.49. Ketorolac is quite lipophilic with a log PC (partition coefficient) value of 2.72 (Muchowski *et al.*, 1985). Ketorolac tromethamine is extremely stable in aqueous solutions at pH 4-8, with a very long shelf-life at 25 °C (L. Gu *et al.*, 25 1988 a); however, it is light sensitive with decarboxylation, especially in the presence of oxygen (L. Gu *et al.*, 1988 b), and ketorolac solutions should be protected from light exposure. The free acid of ketorolac in methanol exhibits

- 4 -

UV absorption maxima at 245 nm and 312 nm, with molar absorptivities of 7080 and 17400, respectively (Franco *et al.* 1982).

Solubility of ketorolac tromethamine in various vehicle systems has been measured by Yu *et al.* (1988). Certain of the solubilities are given below.

5	Vehicles	Solubilities (mg/ml)
	water	725
	propylene glycol (PG)	200
10	PG (50 %), Oleic acid (50 %)	110

The analgesic property of ketorolac tromethamine, like that of other non-steroidal anti-inflammatory drugs, appears to result from cyclo-oxygenase inhibition by way of action on inhibition of prostaglandin synthesis (Buckley *et al.* (1990)). Ketorolac tromethamine has high analgesic and anti-inflammatory potency; administered orally, the analgesic potency of ketorolac tromethamine is about 3-6 times that of indomethacin, about 25-50 times that of naproxen, and about 180 times that of aspirin, and the anti-inflammatory potency of ketorolac tromethamine is about 2-3 times that of indomethacin or naproxen.

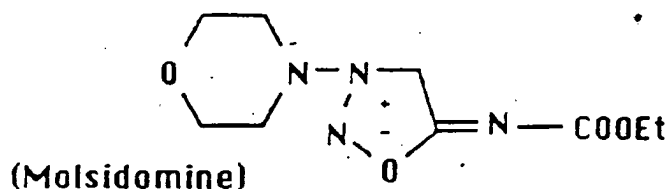
Yu *et al.* (1988) describes percutaneous absorption of ketorolac and ketorolac tromethamine in Rhesus monkeys using a number of solution formulations. Two vehicle combinations (propylene glycol and linoleic acid, and propylene glycol and oleic acid) were shown to be effective in enhancing percutaneous absorption of both ketorolac and ketorolac tromethamine. High C_{max} values were achieved within 8 hours.

3. Molsidomine.

Molsidomine is a vasodilator, useful for example in treatment of angina pectoris.

- 5 -

Molsidomine (N-5-ethoxycarbonyl-3-morpholinosydnonimine) is a sydnonimine derivative having a mesoionic aromatic ring. It is also an ester prodrug. Its chemical structure is shown below:



10

Molsidomine is a white colorless crystal powder, practically tasteless or odorless. The imine has a molecular weight of 242 with a melting point of 140-141 °C and a pK_a value of 3.34 at 25 °C. It exhibits a UV absorption maximum at 326 nm in $CHCl_3$. The solubilities (saturated) of molsidomine in various solvent systems, as reported in Yamada *et al.* (1987), *Chem. Pharm. Bull.*, Vol. 35, pp. 3399-406, are shown below.

Vehicles Solubilities at 25°C (%)

20

Glycol salicylate	15.1
Propylene glycol	6.37
PEG 400	5.23
Glycerin	1.80
25 Oleic Acid	1.37
Octyl.decyl oil	0.36
Isopropyl myristate	0.09

30

Molsidomine is known to be freely soluble in $CHCl_3$; soluble in dilute HCl, ethanol, ethyl acetate, methanol; sparingly soluble in water, acetone,

- 6 -

benzene; very slightly soluble in ether, petroleum ether, Merck Index, 10th edition, page 892 (1983). It is soluble in propylene glycol and a variety of organic solvents. The chemical stability of molsidomine has been investigated in detail by Asahi *et al.* (1971), *Chem. & Pharm. Bull.*, Vol. 19, pp. 1079-88, as shown below.

	pH	t ₉₀ (days) at 20°C
10	1 - 2	38
	4	250
	5 - 7	950 (2.6 years)
	10	400
	11	40

15

Molsidomine is photosensitive, particularly in sunlight.

Molsidomine has been shown to possess a sustained anti-anginal effect and can be metabolized to SIN-1, which is readily converted into the active metabolite SIN-1A (carries a free nitroso group).

20

A very recent investigation on the vasodilation action of molsidomine and other vasodilators, including nitroglycerine reveals that it is the nitric oxide, liberated from the active metabolite SIN-1A, that activates the soluble guanylate cyclase, which in turn causes vasodilation. This is a major difference from the vasodilation action of nitroglycerin.

25

The coronary vasodilation action of nitroglycerin depends on the presence of cysteine. Cysteine deficiency was found to be associated with tolerance developed for nitroglycerin uses. After prolonged exposure to nitroglycerin, tolerance toward the drug developed in coronary strips can be antagonized by cysteine. However, the active metabolite of molsidomine, SIN-1A, is active in both the presence and the absence of cysteine; therefore, molsidomine produces

30

insignificant tolerance (Kulovetz *et al.* (1985), making it a better alternative for anti-anginal therapy.

In *in vivo* studies of transdermal delivery of molsidomine in rats, a combination of propylene glycol with 10 % oleic acid produced an estimated
5 flux of 399 $\mu\text{g/hr-cm}^2$ for molsidomine (Yamada *et al.* (1987) *Chem. Pharm. Bull.*, Vol. 35(8), pp. 3390-98).

A single oral dose of 2 mg of molsidomine can produce anti-anginal effects in patients with coronary heart disease for 3 to 5 hours (J. Ostrowski
et al. (1985) *Am. Heart Jour.*, pp. 641-43). Different oral dosing levels can
10 benefit patients having different degrees of coronary heart disease. Typically, oral doses of 2 mg three times daily, or 4 mg four times daily are suggested. Pharmacokinetic data indicate that the total clearance and peak plasma concentration of molsidomine were 46,000 ml/hr and 15 mg/ml, respectively, following administration of an oral dose of 2 mg. The bioavailability of
15 molsidomine from oral doses is 44 %. Generally, the effective blood concentration of a drug is less than the peak plasma concentration; therefore, an estimation of target flux based on the effective blood concentration should be a better indication of the delivery rate required to produce therapeutic response.

European Patent Publication No. EP 0 127 468 A1 describes
20 percutaneous formulations containing various amounts of molsidomine and various absorption promoters.

Summary of the Invention

We have discovered that certain monolithic acrylic matrix formulations
25 can be effective in transdermal delivery of active agents. By way of examples, we have discovered that ketorolac tromethamine and molsidomine can be effectively delivered transdermally using monolithic acrylic latex matrix

- 8 -

formulations according to the invention; particularly, using an accepted *in vitro* model we have demonstrated transdermal delivery of ketorolac tromethamine and of molsidomine from the monolithic acrylic latex matrix compositions of the invention at skin flux rates suitable for therapeutic use. The acrylic latex
5 matrix formulations of the invention have low skin irritation scores.

Disclosure of the Invention

Accordingly, in one general aspect the invention features a monolithic matrix formulation for transdermal administration of an active agent, which
10 formulation includes in combination as a copolymer 2-ethylhexyl acrylate, 2-hydroxyethyl methacrylate, and methacrylic acid; and transdermal delivery devices that include such a monolithic matrix formulation.

A "monolithic matrix", as that term is used herein, is the material, typically in the form of a film or gel, in a transdermal drug delivery system that
15 contains the active agent to be delivered and a vehicle or vehicle combination, which may include an enhancer, and from which the active agent passes. A "monolithic matrix formulation", as that term is used herein, is the combination of components used to form a monolithic matrix.

In preferred such embodiments the monolithic matrix formulation includes
20 as a copolymer the following:

2-ethylhexyl acrylate	60 - 95 wt. %
2-hydroxyethyl methacrylate	5 - 25 wt. %
methacrylic acid	0.5 - 10 wt. %

In some embodiments, the monolithic matrix formulation includes as a
25 copolymer 2-ethylhexyl acrylate, 2-hydroxyethyl methacrylate, methacrylic acid and acrylic acid. In preferred such embodiments the monolithic matrix formulation includes as a copolymer the following monomers:

- 9 -

2-ethylhexyl acrylate	60 - 98 wt. %
2-hydroxyethyl methacrylate	0.1 - 5 wt. %
methacrylic acid	0.5 - 10 wt. %
acrylic acid	0.5 - 10 wt. %

5 In another general aspect the invention a monolithic matrix formulation for transdermal administration of an active agent, which formulation includes a composition selected from the group consisting of AE 2390 and AE 2616; and transdermal delivery devices that include such a monolithic matrix formulation.

10 In another general aspect the invention features a method for making a monolithic matrix for transdermal delivery of an active agent, including steps of combining the active agent with a selected vehicle or vehicle composition and with the matrix formulation; spreading the resulting material, containing active agent and matrix formulation homogeneously dissolved, dispersed, or suspended in the vehicle, to form a film, and drying the matrix film.

15 In some embodiments for administration of ketorolac tromethamine, and in some embodiments for administration of molsidomine, the vehicle includes polyethylene glycol monolaurate ("PGML") or propylene glycol ("PG") or, more preferably, includes a combination of PGML and PG. The method for making the monolithic matrix for such embodiments includes steps of mixing
20 the active agent with the vehicle, and stirring and warming the mixture; adding the components of the monolithic matrix formulation; stirring and mixing resulting material thoroughly to form a homogeneous suspension, dispersion, or solution; spreading the homogeneous material evenly onto a release liner to form a film; and drying the film.

25 Transdermal delivery devices according to the invention include, in some embodiments, a backing layer, serving to support the monolithic matrix film during manufacture and storage, and while the device is in use; and a

- 10 -

removable release liner, serving during storage to protect those portions of the device that are in contact with the skin when the device is in use.

In another general aspect the invention features a method for administration of an active agent to a subject, including steps of providing a
5 monolithic matrix formulation including in combination as a copolymer 2-ethylhexyl acrylate, 2-hydroxyethyl methacrylate, and methacrylic acid and, in some embodiments additionally acrylic acid; and contacting the active agent-containing monolithic matrix formulation with the subject's skin.

In some embodiments, the active agent is ketorolac tromethamine, and the
10 method includes providing a monolithic matrix according to the invention, containing an effective amount of ketorolac tromethamine; in other embodiments, the active agent is molsidomine, and the method includes providing a monolithic matrix according to the invention, containing an effective amount of molsidomine.

15

Description of Preferred Embodiments

Preferred embodiments of the invention will now be described, beginning with a brief description of the drawing.

Brief Description of the Drawing

The Fig. is a sketch showing a transdermal delivery device including a monolithic matrix according to the invention.

Modes of Carrying out the invention

25 Fabrication of Monolithic Matrices.

Generally, acrylic latex matrix formulations according to the invention are made by suspending or dissolving or dispersing the active agent in a selected vehicle or vehicle composition and mixing with a selected polymer system to

- 11 -

form a homogeneous solution, suspension, or dispersion. The resulting material, containing active agent and polymer system homogeneously dissolved or suspended in the vehicle, is spread into a film and dried. The resulting active agent-containing monolithic matrix film can then be stored until use.

5 Preferably, the material is spread onto a backing layer of a release liner, typically a polymer film, and the film is covered after drying with an additional release liner and stored in a water-impermeable enclosure. With reference now to the Fig., in which a transdermal delivery device according to the invention is shown in transverse section generally at 2, the monolithic matrix film
10 constitutes matrix layer 4, which is affixed to a surface 6 of backing layer 8. The matrix layer 4 contains the active agent to be delivered. When the device is in use on a patient, a surface 10 of matrix layer 4 contacts the surface of the patient's skin, and the active agent passes from the matrix layer at surface 10 onto and through the skin; when the device is in storage, the matrix layer is
15 protected by peelable release liner 12.

As noted above, certain commercially available polymer systems can be suitable for use in constructing monolithic matrices according to the invention. Alternatively, the selected polymer system can be constructed as a copolymer from its monomer constituents according to copolymerization techniques well
20 known in the polymer art. Particularly, in some embodiments the copolymer is a random copolymer formed by emulsion polymerization beginning with the subunits. The resulting polymer system can be provided in emulsion form.

Use.

25 The monolithic matrix formulations according to the invention can be used in the construction of monolithic matrix transdermal delivery devices for administration of any of a variety of active agents. For use, the matrix, containing the active agent and, preferably, supported on a backing layer, is

- 12 -

brought into contact with the subject's skin. The active agent then passes from the matrix into and through the skin.

The monolithic matrix formulations of the invention will now be illustrated by showing the construction and operation of transdermal delivery matrices capable of delivering, by way of examples, molsidomine and ketorolac tromethamine, at skin flux rates suitable for therapeutic use. Other active substances can be effectively transdermally delivered using monolithic matrices according to the invention, including substances that do not pass readily through the skin.

10

Example A

Monolithic Matrix Formulations for Delivery of Ketorolac Tromethamine

By way of example, monolithic matrices containing ketorolac tromethamine and having acrylic latex matrix formulations according to the invention were made, and their delivery rates were demonstrated in an *in vitro* model system.

Generally, the protocol was as follows. An appropriate amount of a combination of the selected vehicle components was weighed into a vial containing a ketorolac tromethamine residue. The vial was warmed and the mixture was stirred to dissolve or suspend the ketorolac tromethamine in the vehicle, and then the components of the selected polymer system were weighed into the vial. The resulting mixture was then mixed using a rotary mixer for a time sufficient to form a homogeneous solution, or suspension, or dispersion of the components, typically at least 1 or 2 hours. The homogeneously mixed wet material was then spread evenly using a Gardner knife onto the backing layer of a release liner (usually a polyethylene plastic sheet) to make a film having a suitable thickness, typically between 20 and 50 mils when wet. Where an organic solvent was used in the mixing steps, the film was allowed to dry on

- 13 -

the backing sheet in a hood for a time, typically at least 20 minutes, and then was further dried for a time in an oven at an elevated temperature, typically 1 to 3 hours at about 70 °C, to form a cured film affixed to the backing sheet. Thereafter the film was cooled to room temperature, a release liner was used to
5 cover the exposed film surface and the film was stored in a plastic bag until use.

More particularly, the following protocol was used to make ketorolac tromethamine-containing monolithic matrices having acrylic latex matrix formulations according to the invention for prototype demonstrations, using an
10 accepted *in vitro* model, of delivery of ketorolac tromethamine.

1. Target Flux of Ketorolac.

It is necessary to combine both the oral dose and the pharmacokinetics data to estimate the target flux of ketorolac. For an oral dosage regimen of ketorolac tromethamine, it is recommended that 10 mg be given every 6 hours
15 as needed for short-term management of moderate to severe pain.

High oral bioavailability of 80 - 100 % has been determined for ketorolac tromethamine. Following an oral administration of 10 mg of ketorolac, the C_{max} of about 0.8 $\mu\text{g/ml}$ was rapidly attained. The total clearance of ketorolac is 1750 ml/hr/70 kg.- From the mean plasma concentration/time profiles of
20 ketorolac after oral administration of 10 mg of ketorolac tromethamine, at the 6 hour time points, the plasma concentration is approximately 0.2 to 0.3 $\mu\text{g/ml}$ (Jung *et al.* (1988), (Jallad *et al.* (1990), (Mroszczak (1990)). The Maintenance Target Flux is therefore estimated to be in the range of 26 to 40 $\mu\text{g/hr/cm}^2$. As the total clearance and the volume of distribution (7.7 lit/70 kg)
25 are small, the Loading Dose of ketorolac tromethamine may not present a problem for reaching the maintaining target flux.

- 14 -

2. Materials.

Ketorolac tromethamine injectables (Toradol) of 60 mg/2 ml were purchased from a local pharmacy. The injectables contain 10% ethanol and sodium chloride adjusted to isotonic conditions. The injectables were adjusted to physiological pH using either HCl or NaOH. Propylene glycol monolaurate ("PGML") used in the skin permeation studies was obtained from Gattefosse (Elmsford, NY). Morstik 607 was obtained from Morton-Thiokol, Silicone 2920 from Dow Corning, and Gelva 2333 from Monsanto. Precoated thin layer chromatography (t.l.c.) plates, obtained from Analtech, were Silica Gel GF with a thickness of 250 microns. Other chemicals used were reagent grades.

Acrylics AE 2616, AE 271, AE 1201 and AE 2390 were obtained from Avery Dennison Chemical Division, Mill Hall, PA. The compositions of AE 2390 and of AE 2616 are reported by Avery as follows:

15

AE 2390

2-ethylhexyl acrylate (CAS # 103-11-7)	60 - 98 wt. %
2-hydroxyethyl methacrylate (CAS # 868-77-9)	0.1 - 5 wt. %
methacrylic acid (CAS # 79-41-4)	0.5 - 10 wt. %
acrylic acid (CAS # 79-10-7)	0.5 - 10 wt. %

20

AE 2616

2-ethylhexyl acrylate (CAS # 103-11-7)	60 - 95 wt. %
2-hydroxyethyl methacrylate (CAS # 868-77-9)	5 - 25 wt. %
methacrylic acid (CAS # 79-41-4)	0.5 - 10 wt. %

25

3. Fabrication of Monolithic Matrices.

An appropriate amount of the vehicle combination (PGML, PG) was weighed into the vial containing the ketorolac tromethamine residue. The vial was warmed and the mixture was stirred into solution or suspension before the

- 15 -

appropriate polymer system was weighed into the vial. Each formulation was then mixed with a rotary mixer for at least 1-2 hours until it formed a homogeneous solution or suspension. The material was spread evenly with a Gardner knife on the backing layer of a release liner such as a polyethylene plastic sheet to make films of various thickness, in the range 20-50 mils (wet). If an organic solvent was involved, the film was allowed to dry in a hood for at least 20 minutes and then further dried in an oven at 70 °C for 1 to 3 hours. After cooling the cured films, a release liner was used to cover the films and they were stored in plastic bags until use.

4. Skin Flux Tests.

Human cadaver epidermis was removed carefully from dermatomed full thickness skin after the skin had been heated in deionized water at 60 °C for one to two minutes. The stripped epidermis was placed between two polyethylene plastic sheets and refrigerated at -20 °C until use. Discs of the epidermis having a diameter of 5/8" were punched out with a die and tested for leakage by soaking the epidermis in water, then spreading it flat on a plastic sheet, and pressing the top of the epidermis lightly a few times with a piece of laboratory tissue. Leakage of the epidermis was detected by appearance of wet spots on the tissue.

Epidermis discs proving to be free of leaks were placed on top of a receiver cell of a modified Franz vertical diffusion cell assembly, and a donor cell was placed on top of the receiver cell. A small magnetic stir bar was inserted through the sampling port into the donor cell compartment. The diffusion cell assemblies were clamped together and transferred to a skin permeation room (controlled at 32 °C). The receiver cell compartments were filled with 8.0 ml of isotonic phosphate buffer, pH 7.0.

For tests of solution formulations, a volume of 0.2 ml of a selected liquid formulation was applied to the donor cell compartments, which were then

- 16 -

sealed using a Teflon plug. For matrix formulations, appropriately sized matrix discs having a diameter of 5/8" were punched with a die. The release liner was removed and the matrix was placed onto the epidermis before the diffusion cell assembly was clamped together. At the appropriate sampling time point, a
5 1.0 ml sample was removed from the receptor compartment, and replaced with 1.0 ml of fresh buffer.

5. Skin Flux Data Treatment.

The quantity of ketorolac tromethamine in each sample was assayed by HPLC analytical methods. In the course of each experiment, the amount of
10 ketorolac tromethamine was corrected after the second time point, as a volume of 1.0 ml of the receiver fluid was removed and replaced with fresh receiver fluid. The cumulative quantity of ketorolac tromethamine in each sampling point was calculated and plotted against the sampling time to give the skin permeation profile. The linear portion of the profile was used to estimate the
15 steady state skin flux by linear regression analysis. Division of the slope of the regression line ($\mu\text{g/hr}$) by the permeation area (0.71 cm^2) gives the steady state skin flux ($\mu\text{g/hr/cm}^2$). The acceptance of the skin flux was based on (i) the standard deviation of the replicated experiments (usually $n = 3$), (ii) visual examination of the permeation profiles, and (iii) the standard deviation of each
20 data point for all of the replicated permeation profiles.

6. Ketorolac Release Tests.

The procedure for testing release of ketorolac tromethamine from the latex matrix films was the same as that for the skin flux experiments except that no skin was used. The samples were analyzed by HPLC analytical methods.
25 Cumulative amounts were plotted against square root of time to give release rates of $\mu\text{g/hr}^{1/2}/\text{cm}^2$.

- 17 -

7. Pretreatment of the Epidermis with Vehicles.

In this study, the epidermis was pretreated separately overnight with propylene glycol or PGML. Untreated skin was used as the control. A matrix made of ketorolac tromethamine, PGML, propylene glycol and acrylic AE 2390 was applied to the treated and untreated epidermis in the skin flux experiments.

8. *In Vitro* Skin Flux from Solution Formulations.

The emphasis of this study has been on achieving a target *in vitro* skin flux of ketorolac tromethamine using safe vehicles and potentially safe acrylic latex matrix formulations. The estimated *in vivo* skin flux of ketorolac tromethamine from solutions was very high in the presence of propylene glycol and oleic acid, or propylene glycol and lauric acid, using a Rhesus monkey as the animal model (Yu *et al.*, 1988). Therefore, after some suitable solvent vehicles were identified to enhance ketorolac skin flux, the efforts were directed toward the development of ketorolac tromethamine matrices.

9. Monolithic Matrices.

After having obtained a very high skin flux of ketorolac from solution formulations (See Table 1), the focus of the investigation has switched to monolithic matrix formulations. There are several solvent combinations which may be used in the development of ketorolac tromethamine matrices. PGML is a proven vehicle for transdermal delivery of active agents, *see, e.g.*, U.S. Patent No. 4,906,463, and is preferred, in combination with PG, for use as a vehicle in monolithic matrices according to the invention.

Results of an initial screening of ketorolac tromethamine delivery characteristics using a variety of polymers are shown in Table 2. A very low skin flux was obtained when ketorolac tromethamine, PGML and PG were incorporated into either Morstik 607, Gelva 2333, adhesives obtained from Adhesives Research (MA 31, BS02 and AS102), and Flexcryn 1625. However,

matrices made with acrylic AE 2390 gave a reasonable flux of $4.7 \mu\text{g/hr/cm}^2$, which was reproducible.

The effects of vehicle loading of PGML and PG from 5 % to 25 % appear to be significant, giving higher skin flux. Much effort was then concentrated on the acrylic AE 2390 polymer system. See Table 3. Loading of both ketorolac tromethamine and PGML has proved to be important in enhancing the skin flux.

Since the target flux of ketorolac ($26\text{--}40 \mu\text{g/hr/cm}^2$) is high, depletion of ketorolac from the matrix can become a problem. For a patch of 20 cm^2 , the amount to be delivered during a 24 hour period ranges from 12.5 to 19.2 mg. To sustain such a high delivery rate, the depletion problem can be met by either of two approaches, namely, (1) loading the matrix with a high concentration of ketorolac tromethamine, or (2) using a thicker matrix.

10. Pretreatment Experiments.

The *in vitro* skin flux results are shown in Table 4. A very high skin flux of $89 \mu\text{g/hr/cm}^2$ was obtained in the early part of the permeation profile using skin which was pretreated with PGML.

In transdermal drug delivery from a matrix device, the release rates of both the drug molecule and the enhancer molecule are very important factors which influence the skin flux. Properly designed solution formulations containing vehicles capable of promoting percutaneous absorption can usually afford a very high skin flux. However, after the vehicles and the drug have been incorporated into a matrix system, the skin flux is often reduced appreciably. It is important to assure an adequate release of both the drug molecules and the enhancer in order to obtain good skin flux.

Although a skin flux of $20 \mu\text{g/hr/cm}^2$ was obtained using an acrylic AE 2390 matrix containing 4.5% ketorolac tromethamine, 15% PGML and 15% PG, it is necessary to investigate the ketorolac tromethamine matrix

- 19 -

further. In order to eliminate the question of PGML release, we performed a pretreatment experiment using the above matrix formulation, on a control skin and a skin pretreated with PG or PGML. The skin flux for both the control and the skin pretreated with PG are similar, indicating that PG was not acting
5 as an enhancer. However, the skin flux for the skin pretreated with PGML was very high in the early part of the permeation profile. Ketorolac was depleted from the matrix, as evidenced by the plateau of the permeation profile after 10 hours. Also, it is interesting to note that the permeation profile looks like a release profile, indicating that the barrier function of the skin has been
10 diminished greatly.

The solution formulations containing PGML and PG gave a very high skin flux. However, in solutions, owing to direct contact with the skin, PGML could exert fast action on the skin. PG is known to be a good solvent for ketorolac tromethamine (Yu *et al.* (1988)). When the solution formulations are
15 replaced with the matrix, PGML must first be released from the matrix before it can act on the skin. This release of PGML is very important to skin flux enhancement.

An important point should be mentioned regarding these pretreatment experiments. To obtain a high skin flux, the matrix device must be fabricated
20 in such a way as to be able to release both the drug and the enhancer at a high rate. This will also reduce lag time.

11. Factorial Design of Experiments.

Variables such as the ketorolac tromethamine and the PGML loadings in a matrix system contribute greatly to the overall *in vitro* skin flux of ketorolac.
25 However, other effects from the interaction of variables can occur and can not be revealed with a single variable design. A factorial design of experiments

- 20 -

can show the effect of each variable as well as the effects of variable interactions.

We have made an attempt to use factorial design of experiments to boost the skin flux of ketorolac. Using a general matrix formulation of ketorolac tromethamine, PGML, PG and acrylic AE 2390, and assuming the polymer is a nonvariable, we have studied a design of 3 variables with 2 levels. The results are shown in Table 5. The skin flux for each formulation was done in triplicate and all the standard deviations were within 18%. In general, low loading of ketorolac tromethamine (1.5 %), PGML (5 %) and PG (5 %) gave a low skin flux. However, high loading of ketorolac tromethamine (6 %), PGML (25 %) and PG (25 %) gave a very high skin flux of $38 \mu\text{g/hr/cm}^2$. This indicates the importance of all three variables, which is further confirmed by the effects of ketorolac tromethamine, PGML and PG. P is a probability factor, the smaller the value relative to the magnitude of the effect, the more significant the effect. The exclamation mark indicates that the effect associated with it is insignificant. The interactions between KT and PGML, PGML and PG, and among KT, PGML and PG appeared to be insignificant, although there was some interaction between KT and PG. The last interaction effect between KT and PG on the skin flux may be due to the solubility effects of PG on ketorolac tromethamine.

In the future design and development of a transdermal therapeutic system using these materials, optimization of the systems can be done by using the proper proportion of materials to achieve the desired functional properties of the systems (skin flux, wearability, physical testing, and stability testing).

12. Ketorolac Release from Matrices.

The release of ketorolac from 9 different types of matrices was investigated. The release rate of ketorolac from silicone 2920, Morstik 607, Gelva 788, MA 31, SB02, and AS102 matrices was very low (Table 6);

- 21 -

therefore, these types of matrices were not pursued further. The low release rates may be due to low ketorolac tromethamine loading, since these matrices are lipophilic, and ketorolac tromethamine is a salt. However, two water based polymers, Gelva 2333 and Flexcyl 1625, showed higher release rates. An increase in PGML or PG loading in the Gelva 2333 matrix did not enhance the release rate. Of all the matrices examined, only the acrylic AE 2390 matrix gave a very high release rate ($211 \mu\text{g/hr}^{1/2}/\text{cm}^2$). This matrix also gave a high skin flux.

13. Other Acrylic Polymer Latex Systems.

Since acrylic AE 2390 works well for ketorolac tromethamine, we screened additional acrylic polymer latex systems. AE 2616, AE 271, AE 1201 and AE 2390 latexes were used to fabricate matrices containing 1.5 % ketorolac tromethamine, 15 % PGML and 15 % PG. These fabricated matrices were subjected to a ketorolac release and a skin flux study using an acrylic AE 2390 matrix as the control. The release and skin flux results are shown in Table 7. The ketorolac release rates from the systems tested (except AE 1201) are comparable with that from AE 2390. The skin flux of ketorolac from the matrices AE 2390 and AE 2616 are comparable. As the loading of ketorolac was increased from 1.5 % to 6 % for AE 2616, the flux also increased to $16.1 \mu\text{g/hr}/\text{cm}^2$.

When the release rates and the skin flux rates obtained from these matrixes are examined, they cannot be correlated directly, although the general trend is that a higher release rate affords a higher flux.

14. Primary Rabbit Skin Irritation.

The mean scores for the primary rabbit skin irritation study are shown in Table 8. Because rabbit skin is sensitive during the spring season when these experiments were conducted, the control (mineral oil) shows a mild irritation score of 1.6. PGML and a combination of PGML and PG both show scores

- 22 -

similar to that of the mineral oil. The solution formulation of ketorolac in PGML and PG, which gives a very high skin flux of ketorolac, shows a low score of 2.3. More importantly, the ketorolac monolithic matrix gives a score lower than that of the mineral oil.

5

Example B

Monolithic Matrix Formulations for Delivery of Molsidomine

Further by way of example, monolithic matrices containing molsidomine and having latex matrix formulations according to the invention were made, and their delivery rates were demonstrated in an *in vitro* model system.

10

Molsidomine-containing monolithic matrices were made using protocols, and were tested using human cadaver skin, generally as described above for ketorolac-containing monolithic matrices. Two formulations, and the resulting skin flux rates, are as follows.

15	Formulations	Skin Flux ($\mu\text{g/hr-cm}^2$)
	Molsidomine (5 %)	6.2 \pm 0.1
	PGML (5 %)	
	PG (5 %)	
20	AE 2390 (79 %)	
	Molsidomine (5 %)	8.1 \pm 0.1
	PGML (15 %)	
	PG (15 %)	
25	AE 2390 (65 %)	

Other Embodiments

Other embodiments are within the claims.

- 23 -

Table 1

IN VITRO SKIN FLUX OF KETOROLAC FROM SOLUTIONS OR SUSPENSIONS

Formulations	Skin Flux $\mu\text{g/hr/cm}^2$
Keto Inj	11.5 ± 0.9
PGML	
KT (90mg)	25.1 ± 2.7
PGML/PG	
10%/90%	
KT (30 mg)	103.2 ± 2.1
KT (210 mg)	106.3 ± 2.2
PGML/DDPO4	
90%/10%	
KT (30 mg)	65.4 ± 10.2
KT(60 mg)	84 ± 7.5
KT(180 mg)	144.7 ± 25.6
Oleic acid	
KT (30 mg)	53.0 ± 4.9
Oleic acid/PG	
10%/90%	
KT (30 mg)	48.4 ± 4.9
PGML/Oleic acid/PG	
5%/5%/90%	
KT (30 mg)	64.7 ± 10.8
PGML/Oleic acid/PG	
10%/10%/80%	
KT (30 mg)	68.3 ± 5.1
PGML/Oleic acid/DDPO4/PG	
5%/5%/5%/85%	
KT (30 mg)	$458 \pm 84.9^*$

*Based on early time points

KT=ketorolac tromethamine; PGML=propylene glycol monolaurate; PG=propylene glycol;

DDPO4=dodecylmonophosphate

Table 2

IN VITRO KETOROLAC SKIN FLUX FROM MONOLITHIC MATRIX
FORMULATIONS

FORMULATIONS	Skin Flux $\mu\text{g/hr/cm}^2$
KT/PGML/PG/Mstk 607	0.8 ± 0.2
1.5%/4.9%/4.9%/88.6%	
KT/PGML/PG/Gelva 2333	0.9 ± 0.2
1.5%/4.9%/4.9%/88.6%	
KT/PGML/PG/MA31	0.3 ± 0.1
1.5%/4.9%/4.9%/88.6%	
KT/PGML/PG/BS02	0.5 ± 0.2
1.5%/4.9%/4.9%/88.6%	
KT/PGML/PG/AS102	0.9 ± 0.3
1.5%/4.9%/4.9%/88.6%	
KT/PGML/PG/Gelva 2333	0.6 ± 0.1
1.5%/9.9%/4.9%/83.7%	
KT/PGML/PG/Gelva 2333	0.5 ± 0.1
1.5%/4.9%/9.9%/83.7%	
KT/PGML/PG/Flexcryn 1625	0.2 ± 0.0
1.5%/4.9%/4.9%/88.6%	
KT/PGML/PG/Acrylic AE 2390	4.7 ± 0.3
4.5%/4.9% /4.9%/86.1%	

KT=Ketorolac Tromethamine

- 25 -

Table 3

VEHICLE LOADING EFFECTS ON THE IN VITRO SKIN FLUX OF
KETOROLAC USING MATRICES CONTAINING 4.3% KETEROLAC
TROMETHAMINE

FORMULATIONS	Skin Flux $\mu\text{g/hr/cm}^2$
PGML/PG/Acrylic AE 2390 4.8%/4.8%/86%	4.3 ± 1.1
PGML/PG/Acrylic AE 2390 9.6%/9.6%/76.6%	9.7 ± 1.1
PGML/PG/Acrylic AE 2390 14.4%/14.4%/67%	12.2 ± 0.9
PGML/PG/Acrylic AE 2390 23.9%/23.9%/47.9%	13.6 ± 2.7

- 26 -

Table 4

**IN VITRO SKIN FLUX OF KETOROLAC USING PRETREATED SKINS
AND A MATRIX® CONTAINING 4.3% OF KETEROLAC TROMETHAMINE**

SKINS	Skin Flux $\mu\text{g/hr/cm}^2$
Control	24.2 ± 4.1
Propylene Glycol Pretreated	26.7 ± 1.6
PGML Pretreated	$89.0 \pm 0.2^*$

* Based on the early points of the permeation profiles

@ PGML/PG/Acrylic AE 2390
14.4%/14.4%/86.0%

- 27 -

Table 5

**IN VITRO SKIN FLUX RESULTS FOR A FACTORIAL DESIGN OF
EXPERIMENTS**

Exp.No.	KT	PGML	PG	Skin Flux $\mu\text{g/hr/cm}^2$
1	1.5%	5%	5%	4.5 ± 0.8
2	6%	5%	5%	7.3 ± 0.5
3	1.5%	25%	5%	15.2 ± 2.0
4	6%	25%	5%	28.3 ± 2.6
5	1.5%	5%	25%	5.7 ± 0.5
6	6%	5%	25%	26.7 ± 2.8
7	1.5%	25%	25%	19.6 ± 0.2
8	6%	25%	25%	38.2 ± 2.3

	p
Effect of Ketorolac = 13.88	0.1432
Effect of PGML = 14.28	0.1393
Effect of PG = 8.72	0.2222
Effect of Ketorolac/PGML = 2	0.6451!
Effect of Ketorolac/PG = 5.9	0.3132
Effect of PGML/PG = -1.6	0.7068!
Effect of Ketorolac/PGML/PG = -3.2	

Table 6

**KETOROLAC RELEASE RESULTS FOR MONOLITHIC MATRICES
CONTAINING 1.5% KETEROLAC TROMETHAMINE**

Formulations	Release Flux ($\mu\text{g/hr}^{1/2}\cdot\text{cm}^2$)
PGML/PG/Sil 2920	low
4.9%/4.9%/88.6%	
PGML/PG/Mstk 607	18.5 ± 0.8
4.9%/4.9%/88.6%	
PGML/PG/Gelva 788	9.1 ± 0.2
4.9%/4.9%/88.6%	
PGML/PG/Gelva 2333	34.1 ± 2.7
4.9%/4.9%/88.6%	
PGML/PG/MA 31	9.2 ± 1.2
4.9%/4.9%/88.6%	
PGML/PG/SB02	2.9 ± 0.2
4.9%/4.9%/88.6%	
PGML/PG/AS 102	5.8 ± 2.7
4.9%/4.9%/88.6%	
PGML/PG/Gelva 2333	20.1 ± 1.9
9.9%/4.9%/83.7%	
PGML/PG/Gelva 2333	25.2 ± 1.3
4.9% /9.9%/83.7%	
PGML/PG/Flexcryl 1625	17.8 ± 0.2
4.9%/4.9%/88.6%	
KT/PGML/PG/Acrylic 103-90B	$211.4 \pm 12.9^*$
4.3%/4.9%/4.9%/88.6%	

*containing 4.3% ketorolac tromethamine

Table 7

KETOROLAC RELEASE AND SKIN FLUX RESULTS
USING ACRYLIC LATEXES

Formulations	Release Flux ($\mu\text{g/hr}^{1/2}/\text{cm}^2$)	Skin Flux ($\mu\text{g/hr}/\text{cm}^2$)
KT/PGML/PG/AE2390 1.5%/15%/15%/68.5%	134.3 \pm 0.6	8.8 \pm 0.7
KT/PGML/PG/AE2616 1.5%/15%/15%/68.5%	94.7 \pm 4.9	6.8 \pm 1.5
KT/PGML/PG/AE2616 6%/20%/15%/59%	-	16.1 \pm 1.3
KT/PGML/PG/AE271 1.5%/15%/15%/68.5%	126.0 \pm 0.8	5.7 \pm 0.6
KT/PGML/PG/AE1201 1.5%/15%/15%/68.5%	42.8 \pm 1.9	1.8 \pm 0.3
KT/PGML/PG/AE2390 1.5%/15%/15%/68.5%	142.3 \pm 8.1	12.4 \pm 1.9

- 30 -

Table 8

PRIMARY RABBIT SKIN IRRITATION STUDY
OF KETOROLAC TROMETHAMINE

Materials	Mean Scores
PGML	1.9
PGML/PG	1.9
90%/10%	
PGML/PG/KT	2.3
10%/84%/6%	
KT/PGML/PG/Acrylic AE 2390	1.3
6%/15%/15%/64%	
PGML/PG/Acrylic AE 2390	1.7
15%/15%/70%	
Drakeol 21 (Mineral Oil)	1.6

Rating:

0	Non-irritating
0-1.9	Mildly irritating
2-5.9	Moderately irritating
6-8	Severely irritating

- 31 -

Claims

1. A monolithic matrix formulation for transdermal administration of an active agent comprising in combination as a copolymer 2-ethylhexyl acrylate, 2-hydroxyethyl methacrylate, and methacrylic acid.
- 5 2. The monolithic matrix formulation of claim 1, said copolymer further comprising acrylic acid.
3. The monolithic matrix formulation of claim 1, said copolymer comprising between 60 and 95 wt. % of 2-ethylhexyl acrylate, between 5 and 25 wt. % of 2-hydroxyethyl methacrylate, and between 0.5 and 10 wt. % of
10 methacrylic acid.
4. The monolithic matrix formulation of claim 2, said copolymer comprising between 60 and 98 wt. % of 2-ethylhexyl acrylate, between 0.1 and 5 wt. % of 2-hydroxyethyl methacrylate, between 0.5 and 10 wt. % of methacrylic acid, and between 0.5 and 10 wt. % of acrylic acid.
- 15 5. A monolithic matrix for transdermal delivery of an active agent, comprising the monolithic matrix formulation of claims 1 or 2, and further comprising a suitable amount of the active agent.
6. The monolithic matrix of claim 5, further comprising a suitable
vehicle.
- 20 7. The monolithic matrix of claim 6 wherein said vehicle comprises PGML.
8. The monolithic matrix of claim 7 wherein said vehicle further comprises PG.
9. A transdermal delivery device comprising the monolithic matrix of
25 claim 5 on a backing layer.
10. A method for making a monolithic matrix for transdermal delivery of an active agent, including steps of
combining the active agent with a selected vehicle or vehicle
composition and with the matrix formulation of claim 1;

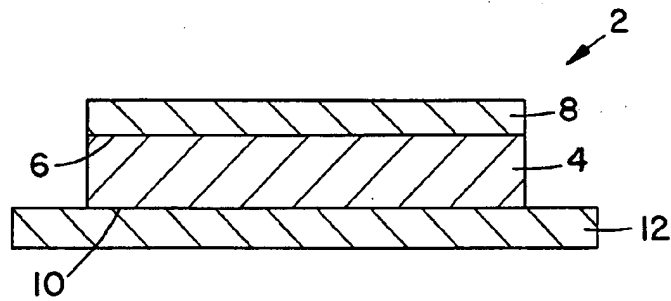
- 32 -

spreading the resulting material, containing active agent and matrix formulation homogeneously dissolved, dispersed, or suspended in the vehicle, to form a matrix film; and
drying the matrix film.

- 5 11. A method for administration of an active agent to a subject, including steps of providing the monolithic matrix of claim 5, and contacting the active agent-containing monolithic matrix with a surface of the subject's skin.
12. The monolithic matrix of claim 5, wherein said active agent
10 comprises ketorolac tromethamine.
13. The monolithic matrix of claim 8, wherein said active agent comprises ketorolac tromethamine.
14. The monolithic matrix of claim 5, wherein said active agent comprises molsidomine.
- 15 15. The monolithic matrix of claim 8, wherein said active agent comprises molsidomine.
16. A monolithic matrix formulation for transdermal administration of an active agent comprising a polymer composition selected from the group consisting of AE 2390 and AE 2616.

20

1 / 1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/07544

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61F 13/02

US CL :424/448

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/448, 449; 514/946, 947

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS transdermal, matrix, ethylhexylmethacrylate, hydroxyethyl methacrylate, methacrylic, ketorolac, molsidomine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 4,751,087 (WICK) 14 June 1988, see column 3, line 30 through column 4, line 20; column 11, line 50 through column 12, line 31.	1-6,9-11,16
X -- Y	US, A, 4,994,267 (SABLOTSKY) 19 February 1991, see column 4, lines 8-58; column 5, line 65; column 6, line 10; column 7, line 38; column 11, lines 33-59; column 25, lines 43-65.	1-6,8-11 ----- 12-16
Y	US, A, 4,568,343 (LEEPER ET AL) 04 February 1986, see entire document.	7

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

*

Special categories of cited documents:

*T

later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

A

document defining the general state of the art which is not considered to be part of particular relevance

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

E

earlier document published on or after the international filing date

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

L

document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O

document referring to an oral disclosure, use, exhibition or other means

P

document published prior to the international filing date but later than the priority date claimed

A

document member of the same patent family

Date of the actual completion of the international search

08 SEPTEMBER 1994

Date of mailing of the international search report

26 SEP 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

D. GABRIELLE PHELAN

Telephone No. (703) 308-2351